4. WORK PLAN AND METHODOLOGY

WORK PLAN FOR BIOEQUIVALENCE STUDY OF GABAPENTIN

1. Literature Review
2. Fasting Bioequivalence Study

- Clinical Phase
  - Preparation of Clinical study Protocol
  - Recruitment of Volunteers and Test Drug
  - Screening of volunteers
  - Conduction of clinical phase
- Bioanalytical Phase
  - Procurement of Working/Reference Standards
  - Bioanalytical Method development for quantification of drug
  - Bioanalytical Method Validation
  - Conduction of Subject sample analysis of fasting study

3. Fed Bioequivalence Study

- Clinical Phase
  - Preparation of Clinical study Protocol
  - Recruitment of Volunteers
  - Screening of volunteers
  - Conduction of clinical phase
  - Bioanalytical Phase
  - Conduction of Subject sample analysis of fed study

4. Statistical Phase

- Statistical analysis of Fasting study
- Statistical analysis of Fed study

5. Final Report Preparation

METHODOLGY FOR BIOEQUIVALENCE STUDY OF GABAPENTIN	
Study design	**AN OPEN LABEL, PIVOTAL, RANDOMIZED, TWO-WAY CROSSOVER, SINGLE DOSE, TWO PERIOD, TWO TREATMENT, TWO SEQUENCE, COMPARATIVE ORAL BIOAVAILABILITY STUDY OF ONE CAPSULE OF GABAPENTIN USP 400 mg OF ALKEM LABORATORIES LIMITED, INDIA WITH REFERENCE PRODUCT ONE CAPSULE OF NEURONTIN® (GABAPENTIN CAPSULE USP 400 mg) OF PFIZER, USA IN HEALTHY ADULT MALE HUMAN SUBJECTS UNDER FASTING OR FED CONDITIONS.**
Background	Gabapentin is originally used for the treatment of epilepsy. Presently, Gabapentin is widely used to relieve pain, especially neuropathic pain. It is structurally related to the neurotransmitter GABA (Gamma-amino-butyric acid). Despite of its structural relationship to GABA and demonstrable antiepileptic activity, the mechanism of action of actions remains uncertain.
Study objectives	The primary objective of this study is to compare the rate and extent of absorption of Gabapentin capsules USP 400 mg of Alkem Laboratories Limited, with Neurontin® (Gabapentin Capsules USP 400 mg) of Pfizer, USA in healthy adult male human subjects under fasting or fed conditions. The secondary objective is to monitor the safety of a single dose of Gabapentin capsules USP 400 mg in healthy adult male human subjects.
Study Design	Balanced, open label, randomized, two treatment, two period, two sequence, single dose, cross over comparative oral bioavailability study in healthy, adult, human male subjects under fasting or fed conditions.
Study Duration	Duration of clinical phase will be 17 days including a wash out period of at least 14 days.
Sample Size	Sufficient number of subjects will be enrolled to dose 48 subjects.

Investigational Drug Products	Test (T)	Gabapentin Capsules USP 400 mg of Alkem Laboratories Limited, India Each capsule contains: 400 mg of Gabapentin USP
	Reference (R)	Neurontin® (Gabapentin Capsules USP 400 mg) of Pfizer, USA Each capsule contains: 400 mg of Gabapentin USP
Screening	Demographic data, medical and medication history, physical examination, 12 lead ECG, vital signs , hematology, Biochemistry, HIV I & II, Hepatitis B & C, urine analysis and Chest X-ray PA view. Drugs of abuse and breathe alcohol test will be performed before check in and each ambulatory samples in each period.	
Confinement	In each period, the subjects will be housed from at least 12 hours before drug administration to 24 hours after drug administration. Subjects will have to visit the clinical facility for 36.0 and 48.0 hrs ambulatory samples.	
Drug Administration Procedure	In each period, after an overnight fast of at least 10 hours, subjects will receive a single dose of Test (T) or Reference (R) product while in sitting posture with about 240 ml of water at ambient temperature according to the randomization schedule But in case of fed study, high fat and high calories breakfast will be provided before dosing.	
Study Restrictions	Water	1.00 hour pre-dose to 1.00 hour post-dose
	Physical Activity	Subjects must be in sitting/semi-inclined posture for the first 02 hours post dose.
	Food	Subjects will not be allowed to eat anything 10 hrs before and 4 hours after dosing. Further diet will be provided at appropriate time. But in case of fed study, high fat and high calories breakfast will be provided before dosing.
PK Sampling	Total 17 samples will be collected from each subject per period at pre-dose (0.0) and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 12.0, 24.0, 36.0, 48.0 hrs post dose.	

Total Blood Loss	Total 34 samples of 5 ml each (170 ml), 5.6 ml discarded blood, 14 ml blood for pre-study screening and 8 ml blood for post study test, amount to total blood loss of approximately 197.6 ml.
Plasma Separation	Blood samples will be centrifuged to separate plasma as soon as possible. The samples will be centrifuged at 4000 rpm, between 8˚C -10˚C for 10 minutes.
Bioanalytical Procedure	The concentration of Gabapentin in plasma will be quantified using LC-MS/MS method according to the regulatory guidelines.
Pharmacokinetic Parameters:	Employing the estimated Plasma concentration time profile of Gabapentin following Pharmacokinetic parameters will be calculated Using SAS Statistical Software (9.1.3 or higher, SAS institute Inc., USA). Primary PK Parameters: $C_{max,}$ AUC_{0-t} and $AUC_{0-\infty}$ and Secondary PK Parameters: K_{el}, T_{max} and $T_{1/2.}$ Descriptive statistics like minimum, maximum, mean, geometric mean, median, standard deviation and coefficient of variation for all pharmacokinetic parameters will be calculated.
Statistical Evaluation:	Summary statistics, ANOVA, intra subject variability, 90% confidence intervals and power will be calculated by non compartmental method using SAS® statistical software (9.1.3 or higher, SAS institute Inc., USA). Bioequivalence between the Test and reference formulations will be assayed by the calculation of the 90 % confidence Interval of test / reference ratio (Least Square Mean) for Cmax, AUC_{0-t} and $AUC_{0-\infty}$ based on Gabapentin (after log transformation) for Gabapentin.
Bioequivalence Criteria	To be considered bioequivalent, T/R ratio & the 90% confidence interval of the primary parameters should fall within the interval 80.00% to 125.00%. The power of the ANOVA to detect a 20% difference (α=0.05) between formulations will be determined.